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NEWS 29 Dec 17  New fields for DPCI
NEWS 30 Dec 19  CAS Roles modified
NEWS 31 Dec 19  1907-1946 data and page images added to CA and CAplus

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=> s adeno-associated viruses or AAV
L1       3153 ADENO-ASSOCIATED VIRUSES OR AAV

=> s adeno associated virus? or AAV
L2       3153 ADENO ASSOCIATED VIRUS? OR AAV

=> s adeno associated virus 2 or AAV-2
L3        536 ADENO ASSOCIATED VIRUS 2 OR AAV-2

=> s l1 or l3
L4       3233 L1 OR L3

=> s l4 and cancer?
L5        201 L4 AND CANCER?

=> s l4 and chemo? resistan?
L6          5 L4 AND CHEMO? RESISTAN?

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L7          2 DUP REM L6 (3 DUPLICATES REMOVED)

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L7  ANSWER 1 OF 2  BIOSIS  COPYRIGHT 2002 BIOSIS      DUPLICATE 1
AN  1999:192567  BIOSIS
DN  PREV199900192567
TI  Enhanced sensitivity of small cell lung cancer cell lines to cisplatin and
    etoposide after infection with adeno-associated virus type 2.
AU  Hillgenberg, M.; Schlehofer, J. R.; von Knebel Doeberitz, M.;
    Klein-Bauernschmitt, P. (1)
CS  (1) Sektion fuer Molekulare Diagnostik und Therapie, Chirurgische
    Universitaetsklinik, Universitaet Heidelberg, INF 120, 69120, Heidelberg
    Germany
SO  European Journal of Cancer, (Jan., 1999) Vol. 35, No. 1, pp. 108-110.
    ISSN: 0959-8049.
DT  Article
LA  English


=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 2 ANSWERS - CONTINUE? Y/(N):y

L7  ANSWER 1 OF 2  BIOSIS  COPYRIGHT 2002 BIOSIS      DUPLICATE 1
AN  1999:192567  BIOSIS
DN  PREV199900192567
TI  Enhanced sensitivity of small cell lung cancer cell lines to cisplatin and
    etoposide after infection with adeno-associated virus type 2.
AU  Hillgenberg, M.; Schlehofer, J. R.; von Knebel Doeberitz, M.;
    Klein-Bauernschmitt, P. (1)
CS  (1) Sektion fuer Molekulare Diagnostik und Therapie, Chirurgische
    Universitaetsklinik, Universitaet Heidelberg, INF 120, 69120, Heidelberg
    Germany
SO  European Journal of Cancer, (Jan., 1999) Vol. 35, No. 1, pp. 108-110.
    ISSN: 0959-8049.
DT  Article
LA  English
AB  In previous studies we have reported the sensitisation of human tumour
    cells to gamma irradiation and chemotherapeutic drugs upon infection with
    the human non-pathogenic adeno-associated virus type 2 ( ***AAV*** -
    ***2*** ) in vitro and in vivo. Treatment of small cell lung cancer
    (SCLC) is consistently hampered by relapses due to the selection of
    ***chemotherapy*** - ***resistant*** cell clones. Hence, we were
    interested to test whether selection of ***chemotherapy*** -
    ***resistant*** SCLC cells might be reduced or even prevented if
    chemotherapy is applied in combination with ***AAV*** - ***2***
    infection. In vitro proliferation assays indicated that the number of
    proliferating cells, after combined treatment with cisplatin and
    etoposide, can be significantly reduced by concomitant ***AAV*** -
    ***2*** infection, as compared with treated but non-infected controls.
    H448 SCLC cells, which show resistance to etoposide/cisplatin chemotherapy
    (compared with a cell line which was never chemotherapeutically treated
    before, like NCI-H209) were significantly more sensitive after ***AAV***
    - ***2*** infection, suggesting that the therapeutic efficacy of
    chemotherapy in SCLC can be enhanced even if the cells are already
    relatively resistant to chemotherapy. Similarly, in vivo growth of tumours
    induced by inoculation of SCLC cells into immunocompromised nude mice was
    reduced more efficiently in ***AAV*** - ***2*** -infected animals
    compared with tumours in mice treated with chemotherapeutic drugs alone.
    These data extend and further support our previous reports on ***AAV***
    functions which might be useful in improving the efficacy of
    chemotherapeutic drugs used in human cancer treatment.

L7  ANSWER 2 OF 2  BIOSIS  COPYRIGHT 2002 BIOSIS      DUPLICATE 2
AN  1997:87547  BIOSIS
DN  PREV199799379260
TI  Gene therapy for haematopoietic and lymphoid disorders.
AU  Kohn, D. B.
CS  Div. Res. Immunol. Bone Marrow Transplantation, Child. Hosp. Los Angeles,
    Mailstop 62, 4650 Sunset Boulevard, Los Angeles, CA 90027 USA
SO  Clinical and Experimental Immunology, (1997) Vol. 107, No. SUPPL. 1, pp.
    54-57.
    ISSN: 0009-9104.
DT  Article
LA  English
AB  Gene transfer into haematopoietic stem cells (HSC) has been investigated
    for treatment of genetic disorders, conferral of ***chemotherapy***
    ***resistance*** and insertion of genes to inhibit HIV-1 replication.
```

Methods have been available for almost a decade to transduce murine HSC using high-titre retroviral vectors and stimulation of HSC proliferation with cytokines such as IL-3 and IL-6. Unfortunately, attempts to replicate the high efficiency of gene transfer using canine or simian gene transfer/bone marrow transplantation models have consistently shown that only a small fraction (0.1-1%) of reconstituting HSC are transduced using protocols similar to those which are successful in murine models. Initial clinical trials using retroviral-mediated gene transfer into human HSC also produced minimal transduction frequencies. The dichotomous results may reflect differences in the cell cycle kinetics of murine HSC versus those of larger mammals or the density of receptors for the retroviral vectors on the cells. Attempts to increase the fraction of HSC which are in active cell cycle, a prerequisite for retroviral-mediated transduction, have used either combinations of recombinant cytokines, culture on marrow stromal layers, or alternative sources for HSC; such as mobilized peripheral blood stem cells or umbilical cord blood. Other efforts have used retroviral vectors packaged with either the Gibbon Ape Leukemia virus envelope or the Vesicular Stomatitis Virus G protein. To date, none of these methods has produced a significantly increased frequency of long-term reconstituting HSC. Results using adeno-associated virus (***AAV***)-based vectors for HSC transduction have been conflicting, with the stable persistence of non-integrated virus particles making interpretation of results difficult using in vitro assays. Therefore, clinical trials may best be directed toward disorders that may benefit from a small fraction of genetically corrected HSC. These would include disorders where progeny of corrected HSC would be expected to have a selective survival advantage (e.g. SCID, WAS, HIV,? chemoresistance) or where a small fraction of corrected cells can have a direct clinical benefit (e.g. CGD, MPS). Further basic research into HSC biology and gene delivery vectors must continue for wider application, such as haemoglobinopathies and some lysosomal storage diseases.

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L1 3153 S ADENO-ASSOCIATED VIRUSES OR AAV
L2 3153 S ADENO ASSOCIATED VIRUSE? OR AAV
L3 536 S ADENO ASSOCIATED VIRUS 2 OR AAV-2
L4 3233 S L1 OR L3
L5 201 S L4 AND CANCER?
L6 5 S L4 AND CHEMO? RESISTAN?
L7 2 DUP REM L6 (3 DUPLICATES REMOVED)

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L8 16 L4 AND (COLON CANCER OR PANCREATIC CARCINOMA OR BRAIN TUMOR OR SMALL CELL LUNG CANCER)

=> s l4 and radiotherapy and resistance
L9 0 L4 AND RADIOTHERAPY AND RESISTANCE

=> s l4 and resistance
L10 170 L4 AND RESISTANCE

=> s l10 and (chemo or radiot?)
L11 1 L10 AND (CHEMO OR RADIOT?)

=> s l10 and radiation
L12 5 L10 AND RADIATION

=> s l11 or l12
L13 6 L11 OR L12

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14 4 DUP REM L13 (2 DUPLICATES REMOVED)

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L14 ANSWER 1 OF 4 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 1
AN 2001287672 EMBASE
TI A hypoxia-regulated adeno-associated virus vector for cancer-specific gene therapy.
AU Ruan H.; Su H.; Hu L.; Lamborn K.R.; Kan Y.W.; Deen D.F.
CS Dr. D.F. Deen, Brain Tumor Research Center, University of California, San Francisco, CA 94143-0520, United States. ddeen@itsa.ucsf.edu
SO Neoplasia, (2001) 3/3 (255-263).
Refs: 35
ISSN: 1522-8002 CODEN: NEOPFL
CY United States
DT Journal; Article
FS 016 Cancer
022 Human Genetics
LA English
SL English
AB The presence of hypoxic cells in human brain tumors is an important factor leading to ***resistance*** to ***radiation*** therapy. However, this physiological difference between normal tissues and tumors also provides the potential for designing cancer-specific gene therapy. We compared the increase of gene expression under anoxia (<0.01% oxygen) produced by 3, 6, and 9 copies of hypoxia-responsive elements (HRE) from the erythropoietin gene (Epo), which are activated through the transcriptional complex hypoxia-inducible factor 1 (HIF-1). Under anoxic conditions, nine copies of HRE (9XHRE) yielded 27- to 37-fold of increased gene expression in U-251 MG and U-87 MG human brain tumor cell lines. Under the less hypoxic conditions of 0.3% and 1% oxygen, gene activation by 9XHRE increased expression 11- to 18-fold in these cell lines. To generate a recombinant adeno-associated virus (rAAV) in which the transgene can be regulated by hypoxia, we inserted the DNA fragment containing 9XHRE and the LacZ reporter gene into an ***AAV*** vector. Under anoxic conditions, this vector produced 79- to 110-fold increase in gene expression. We believe this hypoxia-regulated rAAV vector will provide a useful delivery vehicle for cancer-specific gene therapy.

L14 ANSWER 2 OF 4 BIOSIS COPYRIGHT 2002 BIOSIS
AN 2000:264836 BIOSIS
DN PREV200000264836
TI Enhanced sensitivity of pancreatic tumour cells to 5-FU-chemotherapy mediated by adeno-associated virus type 2 (***AAV*** - ***2***) infection in vitro and in vivo.
AU Eisold, Sven Christian (1); Ridder, Ruediger; Ryschisch, Eduard; Schmidt, Jan; Meyer, Geeske C.; Klar, Ernst; Herfarth, Christian; von Knebel-Doeberitz, Magnus
CS (1) Dept Surg, Univ of Heidelberg, Heidelberg Germany
SO Gastroenterology, (April, 2000) Vol. 118, No. 4 Suppl. 2 Part 1, pp. AGA A531. print..
Meeting Info.: 101st Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Diego, California, USA May 21-24, 2000 American Gastroenterological Association
. ISSN: 0016-5085.
DT Conference
LA English
SL English

L14 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS
AN 1998:642183 CAPLUS
DN 125:292439
TI Improved efficacy of chemotherapy by parvovirus-mediated sensitization of human tumor cells
AU Klein-Bauernschmitt, P.; Von Knebel Doeberitz, M.; Ehrbar, M.; Geletneky, K.; Kleinschmidt, J.; Schlehofer, J. R.
CS German Cancer Research Center, Applied Tumour Virology, Heidelberg, 69120, Germany
SO Eur. J. Cancer, Part A (1998), 32A(10), 1774-1780
CODEN: EJCTEA
DT Journal
LA English
AB Increasing ***resistance*** of tumor cells towards the cytotoxic action of chemotherapeutic drugs is a major limitation in the treatment of cancer patients. The non-pathogenic human adeno-assocd. viruses (***AAV***) have been reported to sensitize HeLa cervical cancer cells to gamma irradn. in vivo and in vitro. To test whether these parvoviruses might render other human tumor cells more sensitive towards chemotherapeutic drugs, we analyzed the effects of ***AAV*** type 2 (***AAV*** - ***2***) infection on established cancer cell lines and freshly explanted tumor biopsies treated with chemotherapeutic agents (e.g. cisplatin). ***AAV*** - ***2*** infection significantly increased the cytotoxic activity of chemotherapeutic drugs compared with uninfected controls. ***AAV*** - ***2*** infection without concomitant chemotherapeutic treatment had no significant effect on viability of the cells. In nude mice, combined application of ***AAV*** - ***2*** infection and chemotherapeutic treatment significantly increased the therapeutic activity on tumors arising from s.c. injected tumor cells compared with tumors treated by chemotherapeutics only. These results indicate that ***AAV*** - ***2*** infection sensitizes human cancer cells towards the cytotoxic action of chemotherapeutic drugs.

L14 ANSWER 4 OF 4 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 92302498 EMBASE
DN 1992302498
TI Modulation of the cellular phenotype by integrated adeno-associated virus.
AU Winocour E.; Puzis L.; Etkin S.; Koch T.; Danovitch B.; Mendelson E.; Shaulian E.; Karby S.; Lavi S.
CS Dept. of Molecular Genetics/Virology, Weizmann Institute of Science,Rehovot, Israel
SO Virology, (1992) 190/1 (316-329).
ISSN: 0042-6822 CODEN: VIRLAX
CY United States
DT Journal; Article
FS 004 Microbiology
037 Drug Literature Index
LA English
SL English
AB The adeno-associated virus (***AAV***) rep gene encodes a series of overlapping, multifunctional, nonstructural proteins (Rep proteins) which regulate the viral life cycle and which are also capable of trans-regulating nonviral gene expressions (reviewed in Berns, 1990, Microbiol. Rev. 54, 316-329). To investigate the expression of the ***AAV*** rep gene in a cellular chromosomal context, SV40-transformed Chinese hamster embryo (OD4) cells were infected with an ***AAV*** /neo hybrid virus and progeny resistant to the antibiotic G418 were selected and amplified. Chromosomal integration and RNA transcription of the ***AAV*** and neo DNA inserts were confirmed by Southern and Northern blotting procedures. One of the G418(R) cell lines stably expressed a protein which reacted specifically with ***AAV*** anti-Rep antiserum in Western immunoblots. The stable integration of ***AAV*** rep DNA, which did not interfere with cell proliferation under normal growth conditions, was associated with two changes in cellular phenotype: eight

of nine lines were markedly more sensitive to UV light (254 nm) than were the parental OD4 cells; and seven of the nine lines had lost the capacity to promote SV40 origin DNA amplification in vitro, in contrast to the parental OD4 cells. OD4 cells transformed to G418(R) by ***AAV*** /neo DNA constructs with a deleted rep gene, or by a neo DNA construct lacking ***AAV*** DNA, did not display these phenotypic changes. It is suggested that stable integration of the ***AAV*** rep gene interferes with cellular processes connected with DNA repair and gene amplification.

=> d his

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L1 3153 S ADENO-ASSOCIATED VIRUSES OR AAV
L2 3153 S ADENO ASSOCIATED VIRUSE? OR AAV
L3 536 S ADENO ASSOCIATED VIRUS 2 OR AAV-2
L4 3233 S L1 OR L3
L5 201 S L4 AND CANCER?
L6 5 S L4 AND CHEMO? RESISTAN?
L7 2 DUP REM L6 (3 DUPLICATES REMOVED)

FILE 'STNGUIDE' ENTERED AT 16:36:04 ON 02 JAN 2002

FILE 'EMBASE, BIOSIS, CAPLUS' ENTERED AT 16:38:10 ON 02 JAN 2002
L8 16 S L4 AND (COLON CANCER OR PANCREATIC CARCINOMA OR BRAIN TUMOR
L9 0 S L4 AND RADIOTHERAPY AND RESISTANCE
L10 170 S L4 AND RESISTANCE
L11 1 S L10 AND (CHEMO OR RADIOT?)
L12 5 S L10 AND RADIATION
L13 6 S L11 OR L12
L14 4 DUP REM L13 (2 DUPLICATES REMOVED)

=> dup rem l8
PROCESSING COMPLETED FOR L8
L15 9 DUP REM L8 (7 DUPLICATES REMOVED)

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YOU HAVE REQUESTED DATA FROM 9 ANSWERS - CONTINUE? Y/(N):y

L15 ANSWER 1 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 1
AN 2001287672 EMBASE
TI A hypoxia-regulated adeno-associated virus vector for cancer-specific gene therapy.
AU Ruan H.; Su H.; Hu L.; Lamborn K.R.; Kan Y.W.; Deen D.F.
CS Dr. D.F. Deen, Brain Tumor Research Center, University of California, San Francisco, CA 94143-0520, United States. ddeen@itsa.ucsf.edu
SO Neoplasia, (2001) 3/3 (255-263).
Refs: 35
ISSN: 1522-8002 CODEN: NEOPFL
CY United States
DT Journal; Article
FS 016 Cancer
022 Human Genetics
LA English
SL English
AB The presence of hypoxic cells in human brain tumors is an important factor leading to resistance to radiation therapy. However, this physiological difference between normal tissues and tumors also provides the potential for designing cancer-specific gene therapy. We compared the increase of gene expression under anoxia (<0.01% oxygen) produced by 3, 6, and 9 copies of hypoxia-responsive elements (HRE) from the erythropoietin gene (Epo), which are activated through the transcriptional complex hypoxia-inducible factor 1 (HIF-1). Under anoxic conditions, nine copies of HRE (9XHRE) yielded 27- to 37-fold of increased gene expression in U-251 MG and U-87 MG human ***brain*** ***tumor*** cell lines. Under the less hypoxic conditions of 0.3% and 1% oxygen, gene activation by 9XHRE increased expression 11- to 18-fold in these cell lines. To generate a recombinant adeno-associated virus (rAAV) in which the transgene can be regulated by hypoxia, we inserted the DNA fragment containing 9XHRE and the LacZ reporter gene into an ***AAV*** vector. Under anoxic conditions, this vector produced 79- to 110-fold increase in gene expression. We believe this hypoxia-regulated rAAV vector will provide a useful delivery vehicle for cancer-specific gene therapy.

L15 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2002 ACS
AN 2000:688256 CAPLUS
DN 133:282353
TI Prolactin regulatory element binding (PREB) protein, cDNA and genetic sequences and therapeutic and diagnostic uses thereof
IN Bancroft, Carter F.; Fliss, Makiko; Clelland, Catherine L.
PA Mount Sinai School of Medicine of New York University, USA
SO PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000056756	A2	20000928	WO 2000-US7642	20000323
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
PRAI US 1999-125728	P	19990323		

AB The present invention relates to the discovery of a novel transcription factor called PREB (prolactin regulatory element binding) protein which functions in the kinase-mediated hormonal regulation of prolactin gene expression. The invention based on the discovery and characterization of the rat Preb gene and protein and the identification of a cloned human DNA contg. the human PREB gene. The invention provides for an assay for distinguishiong between different ***brain*** ***tumor*** types whereby PREB transcript levels are quantified. The presence of PREB would be indicate the presence of astrocytoma ***brain*** ***tumor*** cells but not neuroepithelioma or glioma ***brain*** ***tumor*** cells. Also the present invention provides for methods for the treatment of cancers and autoimmune diseases through the inhibition of prolactin gene expression.

L15 ANSWER 3 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 2
AN 2000117450 EMBASE
TI Current status of viral gene therapy for brain tumours.
AU Gupta N.
CS N. Gupta, Univ. Chicago Children's Hospital, 5841 South Maryland Ave., Chicago, IL 60637, United States. ngupta@peds.bsd.uchicago.edu
SO Expert Opinion on Investigational Drugs, (2000) 9/4 (713-726).
Refs: 94
ISSN: 1354-3784 CODEN: EOIDER
CY United Kingdom
DT Journal; General Review
FS 008 Neurology and Neurosurgery
016 Cancer
022 Human Genetics
LA English
SL English
AB Malignant glial rumours represent the majority of primary brain rumours. Despite the use of many adjunctive treatment strategies in addition to surgery, the prospect of cure or even long-term survival is poor. In the last decade, there has been an explosion of interest in the development of delivery systems that will allow the expression of exogenous genes in the CNS. For the most part, these systems are based upon modified viruses. To date, the greatest experience has been with retroviruses, herpes simplex virus 1 (HSV), adenovirus and adeno-associated virus (***AAV***). This review will outline the biology of these viral vectors, modifications permitting in vivo administration and their respective advantages and disadvantages for the treatment of malignant brain rumours. The present obstacles to gene therapy strategies will also be described. To date, no convincing clinical trial has emerged that provides objective proof of the superiority of gene therapy strategies as compared to conventional treatment.

L15 ANSWER 4 OF 9 BIOSIS COPYRIGHT 2002 BIOSIS
AN 2001:122449 BIOSIS
DN PREV200100122449
TI Host range of adeno-associated viral (***AAV***) vectors and implications for ***AAV*** tumor gene therapy.
AU Veldwijk, M. R. (1); Kleinschmidt, J. A. (1); Zeller, W. J. (1); Fruehauf, S.
CS (1) German Cancer Research Center (DKFZ) Heidelberg, Heidelberg Germany
SO Onkologie, (October, 2000) Vol. 23, No. Sonderheft 7, pp. 176. print.
Meeting Info.: Annual Meeting of the German and Austrian Society for Hematology and Oncology Graz, Austria October 21-25, 2000
ISSN: 0378-584X.
DT Conference
LA English
SL English

L15 ANSWER 5 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 3
AN 1999254105 EMBASE
TI Superior gene transfer into solid tumour cells than into human mobilised peripheral blood progenitor cells using helpervirus-free adeno-associated viral vector stocks.
AU Veldwijk M.R.; Schiedlmeier B.; Kleinschmidt J.A.; Zeller W.J.; Fruehauf S.
CS M.R. Veldwijk, German Cancer Research Centre (DKFZ), Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany. m.veldwijk@dkfzheidelberg.de
SO European Journal of Cancer, (1999) 35/7 (1136-1142).
Refs: 29
ISSN: 0959-8049 CODEN: EJCAEL
PUI S 0959-8049(99)00075-1
CY United Kingdom
DT Journal; Article
FS 016 Cancer
022 Human Genetics
037 Drug Literature Index
LA English
SL English
AB Autologous peripheral blood progenitor cell (PBPC) grafts can be contaminated with tumour cells that potentially give rise to relapse following myeloablative therapy and PBPG transplantation. Adeno-associated virus (***AAV***)-based vectors produced by a new adenovirus-free technique are a gene delivery system which may be applicable for tumour cell purging. To test for the host range of these vectors, solid tumours of clinical relevance and normal GD34+ PBPG were selected as target cells for an ***AAV*** -vector, encoding the green-fluorescent protein (GFP) as the indicator gene. At a multiplicity of infection (MOI) of 100:79.94% .+-. 14.36% (mean .+-. SEM) of the connective tissue sarcoma cell line (HS-1) and 64.84% .+-. 6.91% of the cervical carcinoma cell line cells (HeLa-RG) expressed GFP while the other cell lines tested (1 ovarian tumour, 1 germ cell tumour, 1 osteosarcoma, 2 ***small*** ***cell*** ***lung*** ***cancer***) ranged between 2.82% and 11.94%. Optimising the transduction protocol by use of higher MOIs of up to 500 and by pretreatment with the tyrosine kinase inhibitor, genistein, resulted in up to 95.97% and 94.10% green-fluorescent HS-1 and HeLa-RG cells, respectively. In contrast, only 1.39% .+-. 0.51% of the normal haematopoietic GD34+ progenitor cells expressed GFP at a MOI of 100. The differential infectivity between HS-1 and GD34+ cells was maintained after tumour cell spiking in leucapheresis products. Our observations suggest that ***AAV*** -based vectors may prove useful for purging of autologous PBPG grafts from solid tumour cells.

L15 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2002 ACS
AN 2000:24267 CAPLUS
DN 132:288168
TI HSV-1-based vectors for gene therapy of neurological diseases and brain tumors: Part II. Vector systems and applications
AU Jacobs, Andreas; Breakefield, Xandra O.; Fraefel, Cornel
CS Department of Neurology at the University, MPI for Neurological Research, Cologne, 50931, Germany
SO Neoplasia (N. Y.) (1999), 1(5), 402-416
CODEN: NEOPFL; ISSN: 1522-8002
PB Stockton Press
DT Journal; General Review
LA English
AB A review with 202 refs.. Many properties of HSV-1 are esp. suitable for using this virus as a vector to treat diseases affecting the central nervous system (CNS), such as Parkinson's disease or malignant gliomas. These advantageous properties include natural neurotropism, high transduction efficiency, large transgene capacity, and the ability of entering a latent state in neurons. Selective oncolysis in combination with modulation of the immune response mediated by replication-conditional HSV-1 vectors appears to be a highly promising approach in the battle against malignant glioma. Helper virus-free HSV/ ***AAV*** hybrid amplicon vectors have great promise in mediating long-term gene expression

in the PNS and CNS for the treatment of various neurodegenerative disorders or chronic pain. Current research focuses on the design of HSV-1-derived vectors which are targeted to certain cell types and support transcriptionally regulatable transgene expression. Here, we review the recent developments on HSV-1-based vector systems and their applications in exptl. and clin. gene therapy protocols.
RE.CNT 202
RE
(2) Aboody-Guterman, K; NeuroReport 1997, V8, P3801 CAPLUS
(3) Adams, P; Semin Cancer Biol 1995, V6, P89 CAPLUS
(4) Advani, S; Gene Ther 1998, V5, P160 CAPLUS
(5) Aghi, M; J Natl Cancer Inst 1998, V90, P370 CAPLUS
(7) Andersen, J; Cell Mol Neurobiol 1993, V13, P503 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 7 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 4
AN 1999062500 EMBASE
TI Enhanced sensitivity of ***small*** ***cell*** ***lung*** ***cancer*** cell lines to cisplatin and etoposide after infection with adeno-associated virus type 2.
AU Hillgenberg M.; Schlehofer J.R.; Von Knebel Doeberitz M.; Klein-Bauernschmitt P.
CS P. Klein-Bauernschmitt, Sekt. Molekulare Diagnostik Therapie, Chirurgische Universitatsklinik, Universitat Heidelberg, 69120 Heidelberg, Germany. p.klein@dkfzheidelberg.de
SO European Journal of Cancer, (1999) 35/1 (106-110).
Refs: 21
ISSN: 0959-8049 CODEN: EJCAEL
PUI S 0959-8049(98)00275-5
CY United Kingdom
DT Journal; Article
FS 004 Microbiology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
037 Drug Literature Index
LA English
SL English
AB In previous studies we have reported the sensitisation of human tumour cells to gamma irradiation and chemotherapeutic drugs upon infection with the human non-pathogenic adeno-associated virus type 2 (***AAV*** - ***2***) in vitro and in vivo. Treatment of ***small*** ***cell*** ***lung*** ***cancer*** (SCLC) is consistently hampered by relapses due to the selection of chemotherapy-resistant cell clones. Hence, we were interested to test whether selection of chemotherapy-resistant SCLC cells might be reduced or even prevented if chemotherapy is applied in combination with ***AAV*** - ***2*** infection. In vitro proliferation assays indicated that the number of proliferating cells, after combined treatment with cisplatin and etoposide, can be significantly reduced by concomitant ***AAV*** - ***2*** infection, as compared with treated but non-infected controls. H446 SCLC cells, which show resistance to etoposide/cisplatin chemotherapy (compared with a cell line which was never chemotherapeutically treated before, like NCI-H209) were significantly more sensitive after ***AAV*** - ***2*** infection, suggesting that the therapeutic efficacy of chemotherapy in SCLC can be enhanced even if the cells are already relatively resistant to chemotherapy. Similarly, in vivo growth of tumors induced by inoculation of SCLC cells into immunocompromised nude mice was reduced more efficiently in ***AAV*** - ***2*** -infected animals compared with tumours in mice treated with chemotherapeutic drugs alone. These data extend and further support our previous reports on ***AAV*** functions which might be useful in improving the efficacy of chemotherapeutic drugs used in human cancer treatment.

L15 ANSWER 8 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 97105758 EMBASE
DN 1997105758
TI Cellular and molecular neurosurgery: Pathways from concept to reality - Part II: Vector systems and delivery methodologies for gene therapy of the central nervous system.
AU Zlokovic B.V.; Apuzzo M.L.J.; Neuwelt E.A.; Piepmeier J.M.; Black P.M.
CS Dr. B.V. Zlokovic, 2025 Zonal Avenue, Los Angeles, CA 90033, United States
SO Neurosurgery, (1997) 40/4 (805-813).
Refs: 51
ISSN: 0148-396X CODEN: NRSRDY
CY United States
DT Journal; General Review
FS 008 Neurology and Neurosurgery
022 Human Genetics
037 Drug Literature Index
LA English
SL English
AB DIFFERENT VECTOR SYSTEMS that have been used and/or specifically developed for central nervous system (CNS) gene transfer studies are briefly discussed along with their advantages and disadvantages with respect to potential clinical application. These include retroviruses, recombinant herpes simplex virus, adenoviruses, ***adeno*** - ***associated*** ***viruses*** , encapsulation of plasmid deoxyribonucleic acid into cationic liposomes, and neural and oligodendroglial stem cells. Particular attention has been paid to relate the modality of a specific CNS gene therapy to the strategy for adequate delivery of genetic material to the brain for either global or localized CNS neurodegenerative chronic disorder, as well as for CNS tumors and stroke. Techniques to circumvent the 'impermeable' blood-brain barrier and how to breach the more versatile blood- ***brain*** - ***tumor*** barrier to deliver the genetic material to the target CNS cells are reviewed and include the following: 1) local stereotactic CNS injection/infusion of viral vectors, administration of vector producer cells, or cell replacement; 2) local administration of genetic material into the cerebrospinal fluid ventricudocisternal system; 3) osmotic opening of the blood-brain barrier; 4) local intra-arterial infusion; and 5) administration of blood-***brain*** - ***tumor*** barrier permeabilizers, such as a bradykinin B2 agonist RMP-7. It is concluded that gene therapy for several brain disorders holds great potential, as suggested mainly by in vitro experiments and, to some extent, by a limited number of animal experiments. However, several drawbacks currently hamper the application of gene therapy under the clinical setting. The problems associated with gene therapy that still present major obstacles are as follows: 1) inefficient transfection of host cells by viral vectors; 2) restricted delivery of genetic material across vascular barriers of the CNS and brain tumors; 3) nonselective expression of the transgene; and 4) in situ CNS regulation of the transgene expression in a therapeutically controlled manner, as imposed by the course and phenotype of the CNS disease.

L15 ANSWER 9 OF 9 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 96362402 EMBASE
DN 1996362402
TI Gene therapy against an experimental glioma using adeno-associated virus vectors.
AU Okada H.; Miyamura K.; Itoh T.; Hagiwara M.; Wakabayashi T.; Mizuno M.; Colosi P.; Kurtzman G.; Yoshida J.
CS Department of Neurosurgery, Nagoya University School of Medicine, 65 Tsurumai-cho,Showa-ku, Nagoya 466, Japan
SO Gene Therapy, (1996) 3/11 (957-964).
ISSN: 0969-7128 CODEN: GETHEC
CY United Kingdom
DT Journal; Article
FS 004 Microbiology
016 Cancer
022 Human Genetics
LA English
SL English
AB The efficacy of gene therapy for glioma was examined using adeno-associated virus (***AAV***)-based vectors to deliver genes to experimental tumors in mice. Stereotactic injection of 2 x 105 U-251SP human glioma cells into the brains of nude mice produced tumors of 19.06 +- 1.79 mm2 17 days after injection. Employing a higher titer preparation of ***AAV*** vector containing the gene for beta-galactosidase (***AAV*** -lacZ), dose-dependent transduction of U-251SP cells was seen in vitro. When 1.6 x 1010 ***AAV*** -lacZ particles were directly injected into tumors in vivo, 30-40% of the cells along the needle track expressed beta-galactosidase. Transduction of U-251SP cells in vitro with an ***AAV*** vector containing a bicistronic gene encoding both herpes simplex thymidine kinase and human interleukin-2 (***AAV*** -tk-IRES-IL2) rendered them sensitive to the cytocidal effects of ganciclovir (GCV) and IL-2 was produced in a dose-dependent manner. Cocultures of ***AAV*** -tk-IRES-IL2 transduced cells and nontransduced cells proved highly sensitive to GCV indicating the contribution of the bystander effect. Stereotactic delivery of 6 X 1010 ***AAV*** -tk-IRES-IL2 particles into day 7 tumors in nude mice followed by administration of GCV for 8 days, resulted in a 35-fold reduction in the volume of tumors compared with controls. Normal brains did not suffer from any toxic effect of the administration of ***AAV*** -tk-IRES-IL2 and GCV. These results indicate that high titer ***AAV*** vector treatment may be safe and effective for in vivo gene therapy of human brain tumors.

=> d his

(FILE 'HOME' ENTERED AT 16:29:22 ON 02 JAN 2002)

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 16:29:46 ON 02 JAN 2002
L1 3153 S ADENO-ASSOCIATED VIRUSES OR AAV
L2 3153 S ADENO ASSOCIATED VIRUSE? OR AAV
L3 536 S ADENO ASSOCIATED VIRUS 2 OR AAV-2
L4 3233 S L1 OR L3
L5 201 S L4 AND CANCER?
L6 5 S L4 AND CHEMO? RESISTAN?
L7 2 DUP REM L6 (3 DUPLICATES REMOVED)

FILE 'STNGUIDE' ENTERED AT 16:36:04 ON 02 JAN 2002

FILE 'EMBASE, BIOSIS, CAPLUS' ENTERED AT 16:38:10 ON 02 JAN 2002
L8 16 S L4 AND (COLON CANCER OR PANCREATIC CARCINOMA OR BRAIN TUMOR
L9 0 S L4 AND RADIOTHERAPY AND RESISTANCE
L10 170 S L4 AND RESISTANCE
L11 1 S L10 AND (CHEMO OR RADIOT?)
L12 5 S L10 AND RADIATION
L13 6 S L11 OR L12
L14 4 DUP REM L13 (2 DUPLICATES REMOVED)
L15 9 DUP REM L8 (7 DUPLICATES REMOVED)

=> s l4 and (cisplatin or etoposide)
L16 29 L4 AND (CISPLATIN OR ETOPOSIDE)

=> dup rem l16
PROCESSING COMPLETED FOR L16
L17 14 DUP REM L16 (15 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 14 ANSWERS - CONTINUE? Y/(N):y

L17 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2002 ACS
AN 2001:798037 CAPLUS
DN 135:339221
TI Cytotoxic single-stranded DNA agents
IN Raj, Kenneth; Beard, Peter Martin
PA BTG International Limited, UK
SO PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001080840	A2	20011101	WO 2001-GB1795	20010420

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI GB 2000-9887 A 20000420
AB A method of killing a cell that is lacking in effective p53 protein activity, particularly as compared to wild type, is provided. It is characterized in that it comprises delivering to the cell a single stranded DNA including a portion with at least one base, internally located with respect to any 3' and 5' ends of the DNA, that is unbasepaired with another base in a form that is capable of being internalised by the cell.

L17 ANSWER 2 OF 14 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 1
AN 2001325528 EMBASE
TI Adeno-associated virus type 2-mediated transduction of human monocyte-derived dendritic cells: Implications for ex vivo immunotherapy.
AU Ponnazhagan S.; Mahendra G.; Curiel D.T.; Shaw D.R.
CS S. Ponnazhagan, Department of Pathology, LHRB 513, University of Alabama, 701 19th St. South, Birmingham, AL 35294-0007, United States. sponnazh@path.uab.edu
SO Journal of Virology, (2001) 75/19 (9493-9501).
Refs: 56
ISSN: 0022-538X CODEN: JOVIAM
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB Dendritic cells (DCs) are pivotal antigen-presenting cells for regulating immune responses. A major focus of contemporary vaccine research is the genetic modification of DCs to express antigens or immunomodulatory molecules, utilizing a variety of viral and nonviral vectors, to induce antigen-specific immune responses that ameliorate disease states as diverse as malignancy, infection, autoimmunity, and allergy. The present study has evaluated adeno-associated virus (***AAV***) type 2 as a vector for ex vivo gene transfer to human peripheral blood monocyte (MO)-derived DCs. ***AAV*** is a nonpathogenic parvovirus that infects a wide variety of human cell lineages in vivo and in vitro, for long-term transgene expression without requirements for cell proliferation. The presented data demonstrate that recombinant ***AAV***. (rAAV) can efficiently transduce MOs as well as DCs generated by MO culture with granulocyte-macrophage colony-stimulating factor plus interleukin in vitro. rAAV transgene expression in MO-derived DCs could be enhanced by ***etoposide*** , previously reported to enhance ***AAV*** gene expression. rAAV transduction of freshly purified MO followed by 7 days of culture with cytokines to generate DCs, and subsequent sorting for coexpression of DC markers CDla and CD40, showed robust transgene expression as well as evidence of nuclear localization of the rAAV genome in the DC population. Phenotypic analyses using multiple markers and functional assays of one-way allogeneic mixed leukocyte reactions indicated that rAAV-transduced MO-derived DCs were as equivalent to nontransduced DCs. These results support the utility of rAAV vectors for future human DC vaccine studies.

L17 ANSWER 3 OF 14 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 2
AN 2000208402 EMBASE
TI Transduction of hepatocellular carcinoma (HCC) using recombinant adeno-associated virus (rAAV): In vitro and in vivo effects of genotoxic agents.
AU Peng D.; Qian C.; Sun Y.; Barajas M.A.; Prieto J.
CS C. Qian, Div. of Hepatology and Gene Therapy, Department of Internal Medicine, University of Navarra, 31080 Pamplona, Spain. cqian@unav.es
SO Journal of Hepatology, (2000) 32/6 (975-985).
Refs: 51
ISSN: 0168-8278 CODEN: JOHEEC
CY Denmark
DT Journal; Article
FS 016 Cancer
022 Human Genetics
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
AB Background/Aims: Adeno-associated virus (***AAV***) is an attractive tool for gene therapy. Here we investigated the in vitro and in vivo transduction of hepatocellular carcinoma (HCC) cells by an ***AAV*** vector and the efficacy of different strategies to enhance the transduction of the tumor. Methods: Transduction efficiency was determined by analyzing ***AAV*** -mediated .beta.- galactosidase gene (rAAV/lacZ) expression. Results: Adenovirus help or pretreatment of HCC cells with .gamma.-irradiation or with the topoisomerase inhibitor ***etoposide*** resulted in marked enhancement of cell transduction in vitro. In vivo studies in nude mice with subcutaneous HCC tumors showed that HCC cells were not transduced by ***AAV*** vector alone. However, co-infection of the tumor with adenovirus allowed an efficient expression of the reporter gene but only at the sites of vector injection. Previous .gamma.-irradiation of subcutaneous tumors with 1800 rad was able to improve transduction of HCC cells (up to 30%) using recombinant ***AAV*** . Continuous i.p. infusion of ***etoposide*** in buffalo rats harboring HCC tumors in the liver resulted in transduction of normal liver tissue and also of very small neoplastic lesions (<2 mm) but no transduction was observed in tumors bigger than 2 mm. To analyze this phenomenon we determined ***etoposide*** concentration in hepatic tissue. Our results revealed high concentrations of the drug in non-tumoral tissue but almost undetectable levels in big tumor nodules. Conclusions: Our results indicate that while both radiotherapy and ***etoposide*** enhance transduction of tumor cells by rAAV in vitro, only radiotherapy increases tumor transduction in vivo. Our data suggest the existence of a barrier which limits in vivo the diffusion of chemotherapeutic agents to well-established HCC nodules.

L17 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2002 ACS
AN 1999:764174 CAPLUS
DN 132:9629
TI Adeno-associated viral vector-mediated expression of factor VIII activity
IN Cohen, Lawrence K.; Spratt, S. Kaye; Couto, Linda
PA Cell Genesys, Inc., USA
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9961595	A2	19991202	WO 1999-US10472	19990527
WO 9961595	A3	20000127		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 9941858 A1 19991213 AU 1999-41856 19990527
EP 1082445 A2 20010314 EP 1999-925606 19990527
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRAI US 1998-84423 A 19980527
WO 1999-US10472 W 19990527
AB The invention demonstrates that recombinant ***AAV*** (rAAV) vectors may be used to deliver for effective expression a protein with Factor VIII function to treat hemophilia A. The invention provides methods and materials for expressing polypeptides with factor VIII activity comprising administering at least two rAAV vectors encoding different domains of human factor VIII and at least the heavy and light chains.

L17 ANSWER 5 OF 14 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1999113632 EMBASE
TI Enhancement of UV-induced cytotoxicity by the adeno-associated virus replication proteins.
AU Zhou C.; Yang Q.; Trempe J.P.
CS J.P. Trempe, Dept. of Biochemistry/Molec. Biol., Medical College of Ohio, 3035 Arlington Ave., Toledo, OH 43614-5804, United States. jtrempe@mco.edu
SO Biochimica et Biophysica Acta - Gene Structure and Expression, (19 Mar 1999) 1444/3 (371-383).
Refs: 60
ISSN: 0167-4781 CODEN: BBGSD5
PUI S 0167-4781(99)00014-7
CY Netherlands
DT Journal; Article
FS 029 Clinical Biochemistry
LA English
SL English
AB Adeno-associated virus (***AAV***) normally requires co-infection of a helper virus to complete its life cycle. However, under conditions of cellular stress, such as treatment with carcinogens or ultraviolet (UV) light, a permissive intracellular environment is established and ***AAV*** completes its replicative cycle producing low levels of progeny virus. ***AAV*** DNA replication is dependent upon viral replication proteins, Rep78 and Rep68. The detailed mechanism by which these proteins interact with host cell factors is unknown. We have used a cell line (Neo6) that inducibly expresses the ***AAV*** Rep proteins to study their effects on cells that have undergone UV-induced DNA damage. Induction of Rep protein expression immediately after a sub-lethal dose of UV irradiation resulted in rapid cell killing. Those cells that die had chromatin condensation while cellular membranes remained intact, suggesting that concurrent Rep expression and UV damage induces an apoptosis-like response. However, we did not observe any DNA degradation. Thus we believe that the combination of Rep expression and UV irradiation induces cell death that shares some of the characteristics of apoptosis. UV irradiation and Rep expression induced an increase in the level of the CDK inhibitor, p21(Cip), and the appearance of modified forms of both p21(Cip) and Bcl-2. Alteration of normal expression of these cytostatic/apoptotic proteins provides insight into the intracellular targets of the ***AAV*** replication proteins.

L17 ANSWER 6 OF 14 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 3
AN 1999062500 EMBASE
TI Enhanced sensitivity of small cell lung cancer cell lines to ***cisplatin***, and ***etoposide*** after infection with adeno-associated virus type 2.
AU Hilgenberg M.; Schlehofer J.R.; Von Knebel Doeberitz M.; Klein-Bauernschmitt P.
CS P. Klein-Bauernschmitt, Sekt. Molekulare Diagnostik Therapie, Chirurgische Universitatsklinik, Universitat Heidelberg, 69120 Heidelberg, Germany. p.klein@dkfzheidelberg.de
SO European Journal of Cancer, (1999) 35/1 (108-110).
Refs: 21
ISSN: 0959-8049 CODEN: EJCAEL
PUI S 0959-8049(98)00275-5
CY United Kingdom
DT Journal; Article
FS 004 Microbiology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
037 Drug Literature Index
LA English
SL English
AB In previous studies we have reported the sensitisation of human tumour cells to gamma irradiation and chemotherapeutic drugs upon infection with the human non-pathogenic adeno-associated virus type 2 (***AAV*** - ***2***) in vitro and in vivo. Treatment of small cell lung cancer (SCLC) is consistently hampered by relapses due to the selection of chemotherapy-resistant cell clones. Hence, we were interested to test whether selection of chemotherapy-resistant SCLC cells might be reduced or even prevented if chemotherapy is applied in combination with ***AAV*** - ***2*** infection. In vitro proliferation assays indicated that the number of proliferating cells, after combined treatment with ***cisplatin*** and ***etoposide*** , can be significantly reduced by concomitant ***AAV*** - ***2*** infection, as compared with treated but non-infected controls. H446 SCLC cells, which show resistance to ***etoposide*** / ***cisplatin*** chemotherapy (compared with a cell line which was never chemotherapeutically treated before, like NCI-H209) were significantly more sensitive after ***AAV*** - ***2*** infection, suggesting that the therapeutic efficacy of chemotherapy in SCLC can be enhanced even if the cells are already relatively resistant to chemotherapy. Similarly, in vivo growth of tumors induced by inoculation of SCLC cells into immunocompromised nude mice was reduced more efficiently in ***AAV*** - ***2*** -infected animals compared with tumours in mice treated with chemotherapeutic drugs alone. These data extend and further support our previous reports on ***AAV*** functions which might be useful in improving the efficacy of chemotherapeutic drugs used in human cancer treatment.

L17 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2002 ACS
AN 1998:734970 CAPLUS
DN 129:340538
TI Increasing transduction of cells by adeno-associated virus vectors by using DNA metabolism-altering agents
IN Alexander, Ian E.; Russell, David W.; Miller, A. Dusty
PA Fred Hutchinson Cancer Research Center, USA
SO U.S., 12 pp. Cont.-in-part of U.S. 5,604,090.
CODEN: USXXAM
DT Patent

LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5834182	A	19981110	US 1997-750274	19970225
US 5604090	A	19970218	US 1994-254312	19940606
WO 9533824	A1	19951214	WO 1995-US7202	19950605

W: AU, CA, JP, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRAI US 1994-254312 19940606
WO 1995-US7202 19950605

AB This invention includes methods for increasing the efficiency of transduction of cells, including non-dividing cells, by recombinant adeno-assocd. adenovirus (***AAV***) vectors. The methods utilize agents that alter certain aspects of DNA metab., more specifically, that affect DNA synthesis and/or affect repair, that impact on maintenance of chromosomal integrity, and/or that cause damage to the cellular DNA. Agents and vectors can now also be preselected and screened for transducing ability and/or transducing agents for their effect on DNA metab. These agents include tritiated nucleotides such as thymidine, gamma irradn., UV irradn., cis-platinum, ***etoposide*** , hydroxyurea and aphidicolin.

L17 ANSWER 8 OF 14 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998180472 EMBASE
TI Adeno-associated virus gene transfer into renal cells: Potential for in vivo gene delivery.
AU Langer J.C.; Klotman M.E.; Hanss B.; Tulchin N.; Bruggeman L.A.; Klotman P.E.; Lipkowitz M.S.
CS Dr. M.S. Lipkowitz, Nephrology Division, Box 1243, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, New York, NY 10029, United States. mlipkow@smtplink.mssm.edu
SO Experimental Nephrology, (1998) 6/3 (189-194).
Refs: 24
ISSN: 1018-7782 CODEN: EXNEEG
CY Switzerland
DT Journal; (Short Survey)
FS 004 Microbiology
028 Urology and Nephrology
029 Clinical Biochemistry
LA English
SL English
AB The human parvovirus adeno-associated virus (***AAV***), type 2, has a number of features that make it an attractive choice as a vector for gene delivery to the kidney. ***AAV*** vectors permit long-term gene expression in vivo by integration into the host genome, have potential for site-specific integration of chromosome 19, do not express viral genes or generate a cellular immune response, and demonstrate enhancement of gene expression by chemotherapeutic agents that are approved for use in vivo. These properties confer advantages to ***AAV*** over other viral and nonviral methods for gene transfer. Preliminary experiments in our laboratory suggest that ***AAV*** is able to transfer genes to both renal cells in culture and the kidney in vivo. Thus, ***AAV*** has the potential to be an important gene transfer vector for the kidney in vivo.

L17 ANSWER 9 OF 14 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 4
AN 97217501 EMBASE
DN 1997217501
TI Transduction by adeno-associated virus vectors in the rabbit airway: Efficiency, persistence, and readministration.
AU Halbert C.L.; Standaert T.A.; Aitken M.L.; Alexander I.E.; Russell D.W.; Miller A.D.
CS A.D. Miller, Fred Hutchinson Cancer Research Ctr., 1100 Fairview Ave. North, Seattle, WA 98109, United States. dmiller@fhcrc.org
SO Journal of Virology, (1997) 71/8 (5932-5941).
Refs: 44
ISSN: 0022-538X CODEN: JOVIAM
CY United States
DT Journal; Article
FS 004 Microbiology
022 Human Genetics
LA English
SL English
AB The ability of recombinant adeno-associated virus (***AAV***) vectors to integrate into the host genome and to transduce nondividing cells makes them attractive as vehicles for gene delivery. In this study, we assessed the ability of several ***AAV*** vectors to transduce airway cells in rabbits by measuring marker gene expression. ***AAV*** vectors that transferred either a .beta.- galactosidase (.beta.-gal) or a human placental alkaline phosphatase (AP) gene were delivered to one lobe of the rabbit lung by use of a balloon catheter placed under fluoroscopic guidance. We observed vector-encoded .beta.-gal or AP staining almost exclusively in the epithelial and smooth muscle cells in the bronchus at the region of balloon placement. The overall efficiency of transduction in the balloon-treated bronchial epithelium was low but reached 20% in some areas. The majority of the staining was in ciliated cells but was also observed in basal cells and airway smooth muscle cells. We observed an 80-fold decrease in marker-positive epithelial cells during the 60-day period after vector infusion, whereas the number of marker-positive smooth muscle cells stayed constant. Although treatment with the topoisomerase inhibitor ***etoposide*** dramatically enhanced ***AAV*** transduction in primary airway epithelial cells in culture, treatment of rabbits did not improve transduction rates in the airway. Vector readministration failed to produce additional transduction events, which correlated with the appearance of neutralizing antibodies. These results indicate that both readministration and immune modulation will be required in the use of ***AAV*** vectors for gene therapy to the airway epithelium.

L17 ANSWER 10 OF 14 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 5
AN 97061764 EMBASE
DN 1997061764
TI Persistent expression of human clotting factor IX from mouse liver after intravenous injection of adeno-associated virus vectors.
AU Koeberl D.D.; Alexander I.E.; Halbert C.L.; Russell D.W.; Miller A.D.
CS A.D. Miller, Fried Hutchinson Can. Res. Center, 1100 Fairview Avenue North, Seattle, WA 98109, United States. dmiller@fhere.org
SO Proceedings of the National Academy of Sciences of the United States of America, (1997) 94/4 (1426-1431).
Refs: 43
ISSN: 0027-8424 CODEN: PNASA6
CY United States
DT Journal; Article
FS 022 Human Genetics
025 Hematology
LA English
SL English
AB We previously found that gene transduction by adeno-associated virus (***AAV***) vectors in cell culture can be stimulated over 100-fold by treatment of the target cells with agents that affect DNA metabolism, such as irradiation or topoisomerase inhibitors. Here we show that previous .gamma.-irradiation increased the transduction rate in mouse liver by up to 900-fold, and the topoisomerase inhibitor ***etoposide*** increased transduction by about 20-fold. Similar rates of hepatic transduction were obtained by direct injection of the liver or by systemic delivery via tail vein injection. Hepatocytes were much more efficiently transduced than other cells after systemic delivery, and up to 3% of all hepatocytes could he transduced after one vector injection. The presence of wild-type ***AAV*** , which contaminates many ***AAV*** vector preparations, was required to observe a full response to .gamma.-irradiation. Injection of mice with ***AAV*** vectors encoding human clotting factor IX after .gamma.-irradiation resulted in synthesis of low levels of human clotting factor IX for the 5-month period of observation. These studies show the potential of targeted gene transduction of the liver by ***AAV*** vectors for treatment of various hematological or metabolic diseases.

L17 ANSWER 11 OF 14 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 6
AN 96284696 EMBASE
DN 1996284696
TI Improved efficacy of chemotherapy by parvovirus-mediated sensitisation of human tumour cells.
AU Klein-Bauernschmitt P.; Von Knebel Doeberitz M.; Ehrbar M.; Geletneky K.; Kleinschmidt J.; Schlehofer J.R.
CS German Cancer Research Center, Applied Tumour Virology,69120 Heidelberg, Germany
SO European Journal of Cancer Part A, (1996) 32/10 (1774-1780).
ISSN: 0959-8049 CODEN: EJCTEA
CY United Kingdom
DT Journal; Article
FS 004 Microbiology
016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Increasing resistance of tumour cells towards the cytotoxic action of chemotherapeutic drugs is a major limitation in the treatment of cancer patients. The non-pathogenic human ***adeno*** - ***associated*** ***viruses*** (***AAV***) have been reported to sensitise HeLa cervical cancer cells to gamma irradiation in vivo and in vitro. To test whether these parvoviruses might render other human tumour cells more sensitive towards chemotherapeutic drugs, we analysed the effects of ***AAV*** type 2 (***AAV*** - ***2***) infection on established cancer cell lines and freshly explanted tumour biopsies treated with chemotherapeutic agents (e.g. ***cisplatin***). ***AAV*** - ***2*** infection significantly increased the cytotoxic activity of chemotherapeutic drugs compared with uninfected controls. ***AAV*** - ***2*** infection without concomitant chemotherapeutic treatment had no significant effect on viability of the cells. In nude mice, combined application of ***AAV*** - ***2*** infection and chemotherapeutic treatment significantly increased the therapeutic activity on tumours arising from subcutaneously injected tumour cells compared with tumours treated by chemotherapeutics only. These results indicate that ***AAV*** - ***2*** infection sensitises human cancer cells towards the cytotoxic action of chemotherapeutic drugs.

L17 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2002 ACS
AN 1996:87115 CAPLUS
DN 124:108980
TI Increasing transduction of cells by adeno-associated virus vectors by using DNA metabolism-altering agents
IN Alexander, Ian E.; Russell, David W.; Miller, A. Dusty
PA Fred Hutchinson Cancer Research Center, USA
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9533824	A1	19951214	WO 1995-US7202	19950605

W: AU, CA, JP, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

US 5604090	A	19970218	US 1994-254312	19940606
CA 2192214	AA	19951214	CA 1995-2192214	19950605
AU 9526994	A1	19960104	AU 1995-26994	19950605
EP 765387	A1	19970402	EP 1995-922237	19950605

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE

US 5834182	A	19981110	US 1997-750274	19970225

PRAI US 1994-254312 19940606
WO 1995-US7202 19950605

AB Methods are provided for increasing the efficiency of transduction of cells, including non-dividing cells, by recombinant ***AAV*** vectors. The methods utilize agents that alter certain aspects of DNA metab., more specifically, that affect DNA synthesis and/or affect repair, that impact on maintenance of chromosomal integrity, and/or that cause damage to the cellular DNA. Agents and vectors can now also be preselected and screened for transducing ability and/or transducing agents for their effect on DNA metab. These agents include tritiated nucleotides such as thymidine, gamma irradn., UV irradn., cis-platinum, ***etoposide*** , hydroxyurea, aphidicolin, and camptothecin.

L17 ANSWER 13 OF 14 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 7
AN 95185325 EMBASE
DN 1995185325
TI DNA synthesis and topoisomerase inhibitors increase transduction by adeno-associated virus vectors.
AU Russell D.W.; Alexander I.E.; Miller A.D.
CS Fred Hutchinson Cancer Research Ctr.,Seattle, WA 98104, United States
SO Proceedings of the National Academy of Sciences of the United States of America, (1995) 92/12 (5719-5723).
ISSN: 0027-8424 CODEN: PNASA6
CY United States
DT Journal; Article

FS 021 Developmental Biology and Teratology
LA English
SL English
AB Viral vectors based on adeno-associated virus (***AAV***) preferentially transduce cells in S phase of the cell cycle. We recently found that DNA- damaging agents increased the transduction of nondividing cells. However, the optimal concentrations were toxic to cells. Here we show that the transduction of normal human fibroblasts by ***AAV*** vectors is increased by prior exposure to DNA synthesis inhibitors, such as aphidicolin or hydroxyurea, and topoisomerase inhibitors, such as ***etoposide*** or camptothecin. Transduction efficiencies could be increased >300-fold in stationary cultures at concentrations that did not affect cell viability or proliferative potential. Both S-phase and non-S-phase cells were affected, suggesting that cellular functions other than replicative DNA synthesis may be involved. Applying these methods to gene transfer protocols should improve prospects for gene therapy by ***AAV*** vectors.

L17 ANSWER 14 OF 14 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 8
AN 90340734 EMBASE
DN 1990340734
TI Induction of selective DNA amplification and morphological cell transformation in Syrian hamster embryo cells.
AU Klein P.; Pool-Zobel B.L.; Yalkinoglu O.; Schlehofer J.R.
CS German Cancer Research Center, Inst. of Chemotherapy/Toxicol., Im Neuenheimer Feld 280,D-6900 Heidelberg, Germany
SO Mutation Research, (1990) 232/2 (183-190).
CODEN: MUREAV
CY Netherlands
DT Journal; Article
FS 016 Cancer
022 Human Genetics
052 Toxicology
037 Drug Literature Index
LA English
SL English
AB DNA amplification is a frequently observed event in continuous cell lines and in tumors. It is likely that a common mechanism underlies the amplification of specific DNA sequences which confer drug resistance and genes which give a growth advantage to the tumor. To find a correlation between the induction of DNA amplification by chemicals and morphological cell transformation we treated Syrian hamster embryo (SHE) cells with diverse antineoplastic agents of different classes. Analyis of these agents seems to be important since they are potentially carcinogenic and resistance inducing. For the measurement of DNA amplification we established a new system using adeno-associated virus type 2 (***AAV***)-infected primary SHE cells as target cells and amplification of viral DNA as marker of DNA amplification. Simultaneously we determined morphological cell transformation in SHE cells. Our findings demonstrate that there is only a limited correlation between the induction of ***AAV*** DNA amplification and the morphological cell transformation in SHE cells. The newly established system of ***AAV*** DNA amplification appears to be a useful tool for the investigation of drug resistance in target cells of choice.

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Executing the logoff script...

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	SESSION	TOTAL
FULL ESTIMATED COST		101.00	142.72

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	SESSION	TOTAL
CA SUBSCRIBER PRICE		-4.34	-4.34

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